# A Novel Synthesis of β-Sulfinyl- and β-Sulfonyl-Hydroxamic Acids via CsF-Mediated Ring Opening of Substituted β-Lactones

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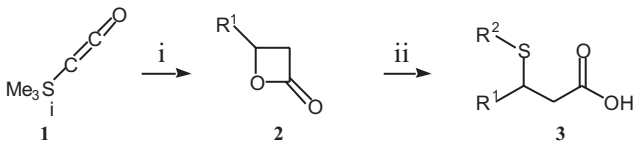
**Abstract:** The ring-opening reaction of 3-substituted β-lactones with thiols was achieved using CsF in DMF as promoter. The resulting β-sulfanyl-carboxylic acid intermediates were coupled to hydroxylamine-Wang resin and the sulfur atom was selectively oxidized to afford β-sulfinyl- and β-sulfonyl-hydroxamic acid libraries.

**Key words:** combinatorial chemistry, solid-phase synthesis, cycloaddition, ring opening, oxidation

The elaboration of selective methods to generate rapidly combinatorial libraries of small molecules useful in medicinal chemistry programs represents a challenge for modern synthetic chemists.[1] Substituted hydroxamic acids are found both in natural and synthetic products that exhibit for example, antibiotic,[2] antiinflammatory[3] or anticancer[4] activities. Due to their broad biological activities hydroxamic acids have motivated the development of a variety of synthetic methodologies to produce combinatorial libraries.[5] We report herein a novel approach to synthesize β-sulfanyl-carboxylic acids **3** from 3-substituted β-lactones **2** using CsF in DMF as promoter and its use to generate β-sulfinyl-hydroxamic acids **5** and β-sulfonyl-hydroxamic acids **6** libraries. These compounds have recently been described to inhibit matrix metalloproteinases, phosphodiesterase[3a] and bacterial peptide deformylase.[2b]

The synthesis started with the $BF_3$•$OEt_2$-catalyzed [2+2] cycloaddition of trimethylsilylketene **1** with aldehydes[6] to afford 3-substituted β-lactones **2** in good yields (Scheme 1). Whilst the reaction proceeded well with non-aromatic aldehydes, the cycloaddition with aromatic aldehydes gave the corresponding α,β-unsaturated carboxylic acids as major product.[7] The ring opening reaction of **2** with thiols was examined using either *i*-$Pr_2$NEt or CsF as activating agents. CsF has been described to promote efficiently the $S_N2$ reaction of secondary mesylates.[8] The reaction promoted by CsF furnished products in higher yield and purity and the undesired α,β-unsaturated carboxylic acids were not observed.

The mild CsF method allowed the introduction of a variety of thiols and the products were obtained by simple filtration of the reaction mixture over silica gel (Table 1). The reaction is expected to be promoted by a composite formed between CsF and DMF.[8] Synthesis of the acids **3** through the base catalyzed Michael addition of thiols with α,β-unsaturated carboxylic acids at elevated temperature[9] gave inferior results.



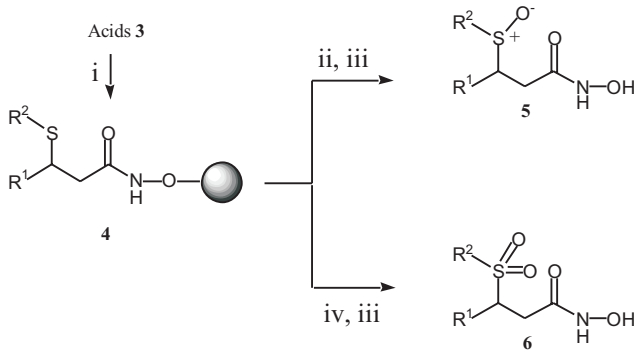

**Scheme 1** i. $BF_3$•$OEt_2$ (0.01 equiv), $R^1$CHO (0.9 equiv), $CH_2Cl_2$, -15°C, 1h. ii. CsF (2 equiv), $R^2$SH (2 equiv, DMF, 30 °C, 1h.

**Table 1** CsF-mediated ring-opening of β-lactones

| -lactone | thiol | product | yield[a] | purity[b] |
|---|---|---|---|---|
| **2a** | SH | **3a** | 57 | 70 |
| **2a** | $H_2N$, SH | **3b** | 25 | 70 |
| **2a** | Cl, Cl, SH | **3c** | 92 | 78 |
| **2b** | SH | **3d** | 84 | 88 |
| **2b** | MeO, SH | **3e** | 89 | 95 |
| **2c** | Br, SH | **3f** | 65 | 95 |
| **2c** | N, N, SH | **3g** | n.d. | 50 |

[a] Yield in% after filtration of the products over silica gel. [b] Purity in% determined by HPLC at 254 nm.

The carboxylic acids **3** were then preactivated by addition of *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5,b]-pyridin-1-ylmethylmethaminium hexafluorophosphate *N*-oxide (HATU)[10] and *i*-$Pr_2NEt$ in *N*,*N*-dimethylacetamide (DMA) and reacted with hydroxylamine-Wang resin (Scheme 2). The resin-bound β-sulfanyl hydroxamic acids **4** were selectively oxidized into their corresponding sulfoxides with 1.1 equiv of *N*-(phenylsulfonyl)-3-phenyloxaziridine[11] in $CH_2Cl_2$. Sulfur oxidation of **4** with 4 equiv MCPBA in $CH_2Cl_2$ furnished the corresponding resin-bound sulfones.




**Scheme 2** i. HATU, *i*-$Pr_2NEt$, DMA, hydroxylamine-Wang resin, r.t., 2 h. ii. *N*-(phenylsulfonyl)-3-phenyloxaziridine (1.1 equiv), $CH_2Cl_2$, r.t., 10 h. iii. TFA:$H_2O$:$CH_2Cl_2$ 70:2:28, 3 h. iv. MCPBA (4 equiv), $CH_2Cl_2$, r.t., 4 h.

**Table 2** Solid-phase synthesis of β-sulfinyl- (**5a**-**5e**) and β-sulfonyl-hydroxamic acids (**6a**-**6f**)

| starting acid | product | yield[a] | purity[b] |
|---|---|---|---|
| **3a** | **5a** | 41 | 95[c] |
| **3b** | **5b** | 71 | 85[c] |
| **3d** | **5c** | 14 | 80[c] |
| **3e** | **5d** | 10 | 95 |
| **3f** | **5e** | 10 | 85[c] |
| **3a** | **6a** | 29 | 95 |
| **3c** | **6b** | 18 | 95 |
| **3d** | **6c** | 14 | 95[c] |
| **3e** | **6d** | 16 | 90 |
| **3f** | **6e** | 26 | 95[c] |
| **3g** | **6f** | 20 | 90 |

[a] Yields in% of purified products are based on the initial loading of hydroxylamine-Wang resin (1.0 mmol/g). [b] Purity in % was determined by HPLC, detecting at 254 nm. [c] Purity in % was determined by $^1H$ NMR.

Cleavage from the resin with TFA:$H_2O$:$CH_2Cl_2$ 70:2:28 afforded the hydroxamic acids **5** and **6**. These compounds were purified by preparative reverse-phase HPLC and obtained in satisfactory yields (Table 2). All new compounds were characterized by HPLC, ESIMS and $^1H$ NMR analysis.[12] The use of hydroxylamine trityl[5d] or *N*-tethered, *O*-protected alkoxyamine[5e] resins instead of hydroxylamine-Wang resin failed to give the desired product in satisfactory yields and purity.

In summary, we have developed a novel and straightforward approach to synthesize β-sulfinyl-hydroxamic acids **5** and β-sulfonyl-hydroxamic acids **6** combinatorial libraries. We have demonstrated for the first time known to us that CsF in DMF is an excellent reagent for the clean ring opening of β-lactones with thiols. The combination of both solution-phase and solid-phase chemistry was particularly useful for rapidly generating the libraries **5** and **6** in sufficient amounts for biological screening.

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(12) The synthesis of **5a** and **6a** are representative of the procedure used for the parallel synthesis of the libraries.
**4-(2,2-Dimethyl-propyl)-oxetan-2-one (2a)**: A solution of $BF_3$•$OEt_2$ (1 mL, 0.5 M, 0.5 mmol) in $CH_2Cl_2$ was slowly added at -15 °C to a solution of 3,3-dimethyl-butyraldehyde (3.9 g, 39 mmol) in $CH_2Cl_2$ (50 mL) and then trimethylsilyl ketene (6 mL, 43 mmol) was added at -15 °C over 30 min. The reaction was stirred for 3 h at -15 °C, two drops of $H_2O$ were added and stirring was continued for 1 h at r.t. After evaporation of the solvent, MeCN (30 mL) and potassium fluoride dihydrate (3 g, 19 mmol) were added. The mixture was stirred overnight, filtered off, evaporated and the residue was chromatographed on $SiO_2$ eluting with hexane/$CH_2Cl_2$/$Et_2O$ (6:2:1) affording **2a**: 4.4 g (80%). $^1$H NMR (250 MHz, DMSO-$d_6$): δ 4.66-4.71 (m, 1H), 3.56-3.72 (m, 1H), 3.64 (dd, J = 5.7 Hz, 16.3 Hz, 1H), 3.19 (dd, J = 4.3 Hz, 16.2 Hz, 1H), 1.75 (dd, J = 7.1 Hz, 14.3 Hz, 1H), 1.66 (dd, J = 5.8 Hz, 14.3 Hz, 1H), 0.93 (s, 9H).
**5,5-Dimethyl-3-(naphthalene-2-sulfanyl)-hexanoic acid (3a)**: Naphthalene-2-thiol (352 mg, 2.2 mmol) was added to CsF (334 mg, 2.2 mmol) in DMF (4 mL), and the suspension was stirred for 10 min at r.t. Then, **2a** (203 mg, 1.1 mmol) was added and the suspension was stirred for 1 h at 30 °C. After filtration of the CsF, the solvent was evaporated, the residue was dissolved in $CH_2Cl_2$/MeOH (95:5) and filtered through silica gel. 189 mg (57%) of **3a**: ESIMS m/z 301.1 ([$M^-$], 100). $^1$H NMR (250 MHz, DMSO-$d_6$): δ 7.88-7.95 (m, 4H), 7.50-7.53 (m, 3H), 3.59-3.63 (m, 1H), 2.45-2.54 (m, 2H), 1.56-1.61 (m, 2H), 0.93 (s, 9H).
**Synthesis of resin 4a**: Hydroxylamine-Wang resin (500 mg, 0.5 mmol, 1% crosslinking, 38-75 μ, 1 mmol/g, from Bachem, Switzerland) was swollen once with DMA (5 mL). To a solution of acid **3a** (226 mg, 0.75 mmol) in DMA (0.75 mL), a solution of HATU in DMA (1.5 mL, 0.5 N, 0.75 mmol) and a solution of *i*-$Pr_2$NEt in DMA (1.5 mL, 1.5 N, 2.25 mmol) were added. After 5 min shaking at r.t., the light yellow solution was added to the hydroxylamine-Wang resin. The reaction mixture was shaken for 2 h, filtered off, washed three times with DMA (4 mL) and three times with *i*-PrOH (3 mL) each. A sample of the resin was dried under high vacuum: 77% conversion based on elemental analysis. ATR (attenuated total reflection) FTIR: ν 1670 $cm^{-1}$. Anal. Found: N, 1.21; S, 1.93.
**5,5-Dimethyl-3-(naphthalene-2-sulfinyl)-hexanoic acid hydroxyamide (5a)**: A portion of resin **4a** (0.25 mmol) was washed three times with $CH_2Cl_2$ (4 mL) and then a solution of *N*-phenylsulfonyl-3-phenyloxaziridine (2.8 mL, 0.1 M, 0.28 mmol) in $CH_2Cl_2$ was added. The reaction mixture was shaken for 10 h, filtered off, washed three times with $CH_2Cl_2$ (4 mL), three times with *i*-PrOH (3 mL) and again three times with $CH_2Cl_2$ (4 mL). A solution of TFA/$H_2O$/$CH_2Cl_2$ 70:2:28 (4 mL) was added to the resin and the reaction mixture was shaken for 3 h. This eluate and one subsequent wash with TFA/$H_2O$/$CH_2Cl_2$ 70:2:28 were collected and combined. The solvent was evaporated and the residue was purified by preparative HPLC (YMC Pack Pro $C_{18}$ column, 5 μ, 120 Å, 50 × 20 mm) using a gradient of $H_2O$ and MeCN (in 3.3 min from 20%MeCN to 95% MeCN, 1.2 min at 95% MeCN, in 0.1 min from 95% MeCN to 20% MeCN, 0.1 min at 20% MeCN, flow: 35 mL/min). 35 mg (41%) of **5a**: ESIMS m/z 332.3 ([$M^-$], 100). $^1$H NMR (250 MHz, DMSO-$d_6$): δ 10.4 (s, 1H, NH), 8.21 (s, 1H), 8.02-8.19 (m, 3H), 7.63-7.70 (m, 3H), 3.12-3.24 (m, 1H), 1.81-2.22 (m, 3H), 1.23-1.31 (m, 1H), 0.93 (s, 9H).
**5,5-Dimethyl-3-(naphthalene-2-sulfonyl)-hexanoic acid hydroxyamide (6a)**: A portion of resin **4a** (0.2 5 mmol) was washed three times with $CH_2Cl_2$ (4 mL) and then of a solution of MCPBA (4.0 mL, 0.25 M, 1.0 mmol) in $CH_2Cl_2$ was added. The suspension was shaken at r.t. for 4 h. Washing of the resin, cleavage of the compound from the resin and purification using preparative HPLC were performed as described for **5a**. 25 mg (29%) of **6a**: ESIMS m/z 348.3 ([$M^-$], 100). $^1$H NMR (250 MHz, DMSO-$d_6$): δ 10.5 (s, 1H, NH), 8.57 (s, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.68-7.79 (m, 2H), 3.56-3.72 (m, 1H), 2.67 (dd, J = 6.8 Hz, 16.1 Hz, 1H), 2.24 (dd, J = 4.4 Hz, 16.1 Hz, 1H), 1.85 (d, J = 13.1 Hz, 1H), 1.32 (dd, J = 7.4 Hz, 14.6 Hz, 1H), 0.72 (s, 9H).

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